B3 word

27. (Amended) The composition according to claim 1 wherein antigen release occurs in the second phase [is] over a period of about 180 days.

REMARKS

The above amendments and following remarks address the rejections outstanding in the parent application at the close of prosecution. Claim 1, 4-9, and 23-27 are pending in the application. Claims 1, 6, and 23-27 have been amended.

Support for the amendments is as follows. Claim 1 has been amended to recite "an emulsion comprising aqueous antigen and a PLGA polymer." This phrase finds support in the specification at least at page 6, line 27 to page 7, line 8. Claim 1 has also been amended to recite "an antigen release profile characterized by three phases." Support for this phrase is found at least at page 23, lines 20-22 (describing release in a "triphasic manner") taken with page 23, lines 22-28 (discussing release in terms of "degradation" and the parameters affecting the "degradation profile." Thus, no new matter is added by any of the amendments.

The amendments are merely clarifying in nature and were not made to distinguish prior art.

Applicants wish to thank the Examiner for courtesies extended during an Examiner Interview on February 11, 1999. Certain § 112 rejections and § 103 rejections were discussed. As set forth in greater detail below, the Examiner indicated that several of the § 112 rejections could be withdrawn.

Drawings

The objections to the drawings are noted. Formal drawings will be filed after receipt of a Notice of Allowance.

Claim Objections

The Examiner objected to Claim 7 on the ground that it fails to comply with 37 C.F.R. § 1.75(b). Specifically, the Examiner indicated that Claim 7 was seen as a duplicate of Claim 6 because both claims recite a composition comprising encapsulated antigen and encapsulated adjuvant. Claim 6 has been amended to recite that "the adjuvant is encapsulated in microspheres," which includes compositions containing adjuvant encapsulated separately from the encapsulated antigen. By contrast, Claim 7 recites that "the adjuvant is coencapsulated with the antigen in the microspheres." Thus, Claims 6 and 7 clearly differ in scope. Withdrawal of the objection is therefore respectfully requested.

Rejections Under 35 U.S.C. § 112, First and Second Paragraphs

Claims 1, 4-9, and 23-27 were rejected under 35 U.S.C. § 112, first paragraph, for failure to satisfy the description requirement.

Specifically, the Examiner indicated that the specification did not provide support phrase "an essentially homogeneous population" in Claim 1. Although Applicants believe that such support is inherent in the specification, this phrase has been deleted from Claim 1 in the interest of expediting prosecution. This aspect of the invention is now recited in Claim 1(e) as follows: "the microspheres have an antigen release profile characterized by three phases," which makes it clear that the microspheres are "an essentially homogeneous population" in that they share a common triphasic release profile.

The specification discusses this concept at page 23, lines 20-31, for example, stating:

> The microspheres of the instant invention are designed to release their contents in a triphasic manner consisting of an initial burst, a slow release, and a second burst. The degradation rate for the

> microspheres of the invention is determined in part by the ratio of lactide to glycolide in the polymer and the molecular weight of the polymer. . . . Furthermore, populations of microspheres designed to have the second burst occur at different times can be mixed together to provide multiple challenges with the antigen and/or adjuvant at desired intervals.

This quotation indicates that a population of microspheres according to the invention is made up of microspheres have common triphasic release profile and that mixtures of such populations provide a more complex release profile. In the example noted in the above quotation, one skilled in the art would understand that mixing two populations that differ in the timing of the second burst would provide a four-phase release profile consisting of an initial burst, a slow release, an initial "second" burst, and a subsequent "second" burst. The more complex release profile of mixed populations contrasts with the triphasic release profile that characterizes the microspheres in a non-mixed or "homogeneous" population.

The Examiner stated that Claim 1's recitation of "beginning at the completion of the second phase" lacked support in the specification. However, support for this phrase is found at least at page 5, lines 30-32 and page 6, lines 10-14 (dividing the period of release into three phases) taken with Figure 8. In Figure 8, the plot of percent cumulative release illustrates that a third phase of rapid release, beginning around day 30, immediately follows a second phase of low-level release.

The Examiner also questioned the support for Claim 1's recitation of an antigen volume "equal to or less than 1 milliliter per 3 grams of polymer." Support for this aspect of the invention is found in the specification at least at page 35. line 33 to page 36, line 2, taken with page 55, lines 39-42. The former passage describes a polymer concentration of 0.3 g/mL and the latter passage describes an aqueous to organic volume ratio of 0.1 mL/mL. Page 16, line 29 to page 17, line 8 establishes that the antigen is in the aqueous phase of an emulsion and the polymer is in the organic phase. A ratio of 0.1 mL aqueous (antigen) phase:1 mL organic (polymer) phase implies that for each 1 mL of aqueous antigen solution, the emulsion contains 10 mL of organic polymer solution. 10 mL of 0.3 g/mL polymer solution contains 3 g polymer.

Therefore, the specification describes an emulsion containing 0.1 mL aqueous antigen for every 3 g polymer.

Claims 1 and 23-27 were rejected on the ground that the specification failed to enable the timing of the second and third phases of the triphasic pattern of antigen release. This rejection was based on the Examiner's belief that "the third phase and the second phase can run anywhere from 190 to 360 days." Office Action, at 4. As explained in the interview, however, Claim 1 recites "a second phase . . . ranging from about 30 to 180 days, and a third phase . . . ranging from about 10 to 30 days." As the specification fully enables the timing of these phases, Applicants respectfully submit that the rejection should be withdrawn.

The Examiner also questioned the support for the timing of the second and third phases. As discussed above, support for "a second phase beginning at the completion of the first phase" is found in the specification at least at page 5, lines 30-32 and page 6, lines 10-14 (dividing the period of release into three phases) taken with Figure 8.

Support for a second phase in which "less than 10 percent of the antigen is released from the microspheres over a period ranging from about 30 to 180 days" is inherent in the specification's description of the timing of the first and third phases, which the specification terms the "initial burst" and the "second burst" (or "autoboost"), respectively. The second phase is the period between the end of the initial burst (first phase) and the beginning of the second burst (third phase). The specification indicates that the initial burst ends after about 1 or 2 days of release. Page 48, line 6 of the specification indicates that the second burst begins at day 30 of release. Subtracting, e.g., 1 day from 30 days gives 29 days as the second-phase period in this exemplary embodiment. Therefore, the specification provides clear support for a second phase extending over about 30 days. Page 47, lines 10-14 of the specification explains how to achieve a second burst ("autoboost") at 180 days ("6 months") from the beginning of release. Subtracting, e.g., 1 day from 180 days gives 179 as the second-phase period in this exemplary embodiment. Therefore, the specification provides clear support for a second phase extending over about 180 days.

Support for a third phase in which "the remaining antigen is released from the microspheres over a period ranging from about 10 to 30 days" is found at least at page 48, line 6 (about 10 days) and line 12 (about 30 days). As the application fully supports the timing of the second and third phases, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Eppstein et al.

Claims 1, 4, 9, and 23-27 stand rejected under 35 U.S.C. § 103 as unpatentable over Eppstein et al., U.S. Patent No. 4,962,091, issued October 9, 1990 ("Eppstein"). The rejection is respectfully traversed.

The Examiner apparently believes that Eppstein teaches all aspects of the claimed invention except "a mean diameter of the microspheres . . . from about 20 to 100 um." The Examiner stated:

> [T]he reference teaches that the rate and duration of release can be varied by the choice of polylactide polymer, molar ratio, intrinsic viscosity and by the shape and configuration of the device. . . . [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.
>
> Therefore, absent evidence to the contrary, the median diameter of the microsphere from about 20 to 100 um is considered routine experimentation.

Office Action, at page 10.

Eppstein teaches "[a]n active agent delivery system for the controlled administration of macromolecular polypeptides which comprises a micro-suspension of water-soluble components in a polylactide matrix." Eppstein, abstract. Eppstein's stated goal is to provide "a more constant rate of polypeptide release throughout the entire operational life of the device than can be obtained with previously known biodegradable systems." Eppstein, at col. 3, lines 57-60.

The Examiner notes that Eppstein discloses multiphasic release. However, Eppstein fails to teach or suggest the antigen release profile recited in Claim 1, which is the only pending independent claim. In particular, Eppstein fails to teach or suggest "a third phase beginning at the completion of the second phase wherein the remaining antigen is released from the microspheres over a period ranging from about 10 to 30 days."

The Examiner has taken the position that one skilled in the art would be motivated to modify the teachings of Eppstein to arrive at the claimed invention. Yet the record is devoid of any such motivation. The Examiner relies on Eppstein for the proposition "that the rate and duration of release can be varied by the choice of polylactide polymer, molar ratio, intrinsic viscosity and by the shape and configuration of the device." Office Action, at 9. However, these five parameters identified by the Examiner could be varied to produce a nearly infinite number of combinations, which would be associated with a variety of release profiles.

Eppstein provides no suggestion of the desirability of the claimed release profile and, consequently, no suggestion of which of the myriad combinations of polylactide polymer, molar ratio, intrinsic viscosity, and device shape and configuration would produce this release profile. First, far from teaching that triphasic release is desirable, Eppstein teaches that release should be constant. Eppstein notes that "[t]he incorporation of large and irregular particles of polypeptide causes an uneven rate of drug delivery, and tends to exacerbate the multiphasic release profiles generally associated with polylactide pharmaceutical preparations." Eppstein, at col. 2, lines 57-61. Eppstein goes on to state: "In contrast, because the polypeptide and other water soluble components of this invention are present as very small and discrete particles within the polylactide matrix, . . . a very regular release profile is achieved which can be made to begin with very little initial lag time, and which is **continuous throughout the life of the system.**" Id. at col. 4, lines 20-27 (emphasis added). Thus, one skilled in the art following the teachings of Eppstein would, if anything, attempt to produce microspheres characterized by continuous, rather than multiphasic, release. Thus, Eppstein unequivocally teaches away from the claimed release profile, which is distinctly multiphasic.

Moreover, assuming arguendo that Eppstein contained some motivation for producing microspheres having a multiphasic release profile, Eppstein contains no motivation for producing microspheres having the claimed profile with the particular percentage release and duration recited for each phase. Because Eppstein fails to recognize the utility of any triphasic release profile, Eppstein cannot reasonably be seen as suggesting the particular benefits associated with the claimed release profile.

Furthermore, Eppstein fails to teach or suggest how to produce microspheres having the claimed release profile. Knowing, in a general sense, that five distinct parameters (polylactide polymer, molar ratio, intrinsic viscosity, and device shape and configuration) affect release would not, without more, lead one skilled in the art to select the specific combination of parameters recited in the claims. Furthermore, Eppstein emphasizes the importance of a sixth parameter, namely the size of polypeptide particles incorporated into the polymer matrix. Therefore, one skilled in the art following the teachings of would, if anything, experiment with this parameter in an effort to achieve sustained release of a particular polypeptide. Applicants submit that this avenue of investigation would not be expected to lead one skilled in the art to the claimed invention.

The Examiner apparently believes that the claimed invention simply represents an optimized version of the microspheres disclosed in Eppstein. However, one seeking to optimize Eppstein's microspheres would adjust parameters known to affect release profile in an effort to **minimize multiphasic release**. This would lead one skilled in the art to select, for the purposes of experimentation, combinations of parameters predicted to yield microspheres having continuous release. By contrast, the recited combination of parameters was found to yield microspheres **having a particular triphasic release pattern** that Applicants found was well-suited for antigen delivery. Applicants submit that "routine experimentation" based on Eppstein cannot possibly entail ignoring what Eppstein teaches should be done and instead experimenting with what Eppstein teaches should be avoided. Nor would it be "routine" to test every possible combination of six different parameters with no particular objective in mind. It is well-settled that "[m]odification unwarranted by the disclosure of a reference is improper," *Carl Schenk,*

A.G. v. Nortron Corp., 218 U.S.P.Q. 698, 703 (Fed. Cir. 1983). Yet the present rejection is based on a modification that finds no support in Eppstein.

During the Examiner Interview, the Examiner stated that the rejection was proper in the absence of any showing of criticality of microsphere diameter, which is the only element of the claimed invention that the Examiner finds lacking in Eppstein. The Examiner clearly understands that microsphere size is one of the important parameters that affect microsphere release profiles. The evidence of record supports this understanding. One of the cited references, Eldridge et al., Mol. Immunology 28:287-94 (1991) ("Eldridge"), notes that multiphasic release profiles can be achieved by mixing "microspheres of two sizes." Eldridge, at 290, col 2. Eldridge further states that "substantially less adjuvancy has been observed with microspheres which are of a size that precludes their uptake by phagocytosis." *Id.* at 293, col. 1. This finding evidences that microsphere size is important in determining suitability for particular applications. Variations in microsphere size produce differences in release profiles due to different interactions with bodily systems as well as the differences observable in release studies in vitro. Therefore, Applicants submit that the claimed microsphere diameter represents a significant distinction over the microspheres disclosed in Eppstein.

Eppstein thus fails to teach or suggest the combination of elements recited in Claim 1 and fails to provide any motivation to experiment in any direction likely to lead to this combination. Accordingly, Applicants submit that Claim 1 is patentable over Eppstein. As Claims 4, 9, and 23-27 depend from Claim 9, these claims are also patentable over Eppstein for at least the reasons discussed above. Withdrawal of the rejection is therefore respectfully requested.

Sanders et al., Eldridge et al., and Jeffery et al.

The Examiner also rejected Claims 1, 4, 9, and 23-27 under § 103 as unpatentable over Sanders et al., J. Pharmaceutical Sciences 73:1294-97 (1984) ("Sanders"), in view of

Eldridge, and further in view of Jeffery et al., Pharmaceutical Research 10:362-68 (1993). The rejections is respectfully traversed.

The Examiner states:

> Sanders et al . . . teach a composition comprising poly(D-L-glycolide) (PLGA) microspheres and an encapsulated analogue of luteinizing hormone releasing hormone. . . .
>
> Sanders et al also teach that the microspheres have a triphasic release over 90 days in which an initial burst is followed by a latent period of 25 days during which less than 0.4 ug/day of the analogue is released, followed by a final release from about day 38 to day 90 as the polymer erodes...However, Sanders et al do not specifically teach the incorporation of an antigen in the microspheres.

Office Action, at pages 10-11. Eldridge is cited as teaching "the use of PLGA as a safe vaccine delivery system," and Jeffery is cited as disclosing encapsulation methods using a variety of aqueous antigen volumes. *Id.* at 12.

Sanders reports studies in which, according to Sanders, a "triphasic release of compound was observed, which was adjusted by altering the critical parameters of the polymer." As has been discussed in previous amendments, Applicants believe that Sanders' data fail to establish triphasic release. The above quotation indicates that the Examiner has relied on the estrus suppression profile shown in Sanders' Figure 4a. While Sanders states that "[t]he system providing the plasma profile (Fig. 4a) demonstrates a clear definition of . . . three phases" (Sanders at 1297, col. 1), Sanders also comments that the estrus suppression model does not provide a reliable indication of the release rate (*Id.* at 1296, col. 1). Therefore, the different "phases" shown in Figure 4a do not necessarily indicate differences in release rates.

Figure 2 of Sanders purports to show an in vivo "release" profile. However, Figure 2 actually shows the percentage of peptide remaining at the site of microsphere injection over a 21-day period. This parameter reflects the movement of microspheres away from the injection site, as well as actual compound release. Therefore, Figure 2 also does not necessarily provide an accurate indication of release rate. The three phases recited in Claim 1 are

characterized by different release rates. Because Sanders lacks credible data regarding release rates, Sanders does not teach or suggest triphasic release within the meaning of Claim 1.

However, even if the data reported in Sanders suggested triphasic release, which Applicants do not concede, nothing in Sanders suggests the particular release profile recited in Claim 1. Specifically, Sanders fails to teach or suggest "a second phase beginning at the completion of the first phase wherein less than 10 percent of the antigen is released from the microspheres over a period ranging from about 30 to 180 days, and a third phase beginning at the completion of the second phase wherein the remaining antigen is released from the microspheres over a period ranging from about 10 to 30 days." Sanders provides no indication of the desirability of this release profile and, consequently, no suggestion of how to achieve it. If anything, Sanders teaches that release should be constant, noting that overall, the release kinetics observed were "quite satisfactory, as indicated by comparison with zero-order kinetics." Sanders, at 1296, col. 2. To the extent that Sanders invites modification, therefore, one skilled in the art would seek to modify the disclosed microspheres to achieve release kinetics that were closer to zero-order. As discussed above for Eppstein, such an objective would lead one skilled in the art away from, not toward, the claimed invention.

Furthermore, as the Examiner recognizes, PLGA microsphere release profiles depend on the interaction of a variety of parameters. Even ignoring Sanders' teaching away from the claimed invention, testing the affects of randomly varying all possible parameters is clearly outside the realm of routine experimentation.

Neither Eldridge nor Jeffery remedy the deficiencies of Sanders. Eldridge discusses "release profiles," but actually discloses anti-toxin antibody titers elicited in response to an encapsulated toxoid vaccine. Moreover, Eldridge considers multiphasic release, but suggests an approach entirely different from that of the claimed invention. Eldridge states:

> This multiphasic release profile could be approached either through the **blending** of vaccine-microspheres with two different copolymer ratios, or by **blending** vaccine microspheres of two sizes.

Eldridge, at 290, col. 1. Eldridge is simply devoid of any recognition that a "non-blended" population of microspheres could have multiphasic release profile analogous to primary and booster immunizations. Nothing in Eldridge or Sanders suggests that Sanders' material would be useful in this context, and even if there references contained such a suggestion, neither Eldridge nor Sanders teach the particular release profile recited in Claim 1 or how the achieve it.

Jeffery discloses no studies of any kind showing triphasic release from microspheres. Moreover, Jeffery focused on smaller microspheres than those of Claim 1. In connection with an experiment that produced larger particles, Jeffery states that, while the use of gelatin in the disclosed "entrapment" process increased entrapment efficiency:

> there was also a considerable increase in particle size (8.1 μm without gelatin to 42 μm with gelatin). Such **an increase in particle size would limit the use of the microparticles as vaccines**.

Jeffery, at 365, col. 2 (emphasis added). Thus, not only does Jeffery fail to teach the claimed release profile, Jeffery also teaches away from the claimed microsphere size.

Sanders, Eldridge, and Jeffery, taken singly or together, fail to teach or suggest the combination of elements recited in the pending claims. Furthermore, these references fail to suggest an avenue of investigation likely to lead to the recited combination of elements. Given the large number of possible release profiles, the selection of the claimed release profile and the discovery of how to achieve it clearly distinguishes the claimed invention from Sanders, Eldridge, and Jeffery. Accordingly, withdrawal of the rejection respectfully requested.

Sanders et al., Eldridge et al., Jeffery et al., and Wang et al.

Claims 5-7 were rejected under § 103 as unpatentable over the combination of Sanders, Eldridge, and Jeffery, in view of Wang et al., J. Controlled Release 17:23-32 (1991) ("Wang"). The rejection is respectfully traversed.

Claims 5-7 depend, directly or indirectly, from Claim 1 and recite a composition "further comprising an adjuvant." The Examiner cited Wang for the proposition that "PLGA microspheres in which bovine serum albumin (BSA) and the adjuvant Carbopol 951 were encapsulated had a higher burst effect release of the BSA and higher daily release of BSA than the microspheres without Carbopol 951." Office Action, at 13. However, Wang does not remedy all the deficiencies of the Sanders-Eldridge-Jeffery combination. Specifically, Wang does not teach or suggest microspheres having a release profile with the recited second and third phases.

In addition, Wang, like Sanders, teaches the desirability of a continuous release profile. Wang states:

> Further studies on drying methods will be required to determine whether it is possible to **reduce the [initial] burst effect without markedly diminishing the normal desired protein release over the first 15 days** of hydrolysis.

Wang, at 29, col. 2. Thus, like the other references of record, Wang provides no motivation to design microspheres that release antigen in distinct initial burst, followed by a phase of relatively low release. Indeed, Wang provides the contrary motivation.

Thus, Claims 5-7 are patentable over combination of Sanders, Eldridge, Jeffery, and Wang because this combination fails to teach all of the elements of the claimed compositions and, if anything, teaches away from the claimed compositions. Withdrawal of the rejection is therefore respectfully requested.

Sanders et al., Eldridge et al., Jeffery et al., Wang et al., and Newman et al.

Claim 8 stands rejected under § 103 as unpatentable over the combination of Sanders, Eldridge, Jeffery, and Wang in view of Newman et al., AIDS Research and Human Retroviruses 8:1413-18 (1992). The rejection is respectfully traversed.

Claim 8 depends from Claim 5, and ultimately therefore from Claim 1. Claim 8 recites a composition "wherein the adjuvant is QS21." Newman is cited simply for its teaching that QS21 "is non-toxic and augments both antibody responses and cell-mediated immunity." Office Action, at 15. Newman does not, however, remedy all the deficiencies of the other references of record. In fact, Newman fails to disclose any of the elements recited in Claim 1(a)-(e). Furthermore, Newman fails to provide any disclosure that would counter the disclosures in Sanders, Eldridge, and Wang that teach away from the claimed invention.

As Claim 8 is clearly patentable over the references of record, Applicants respectfully request withdrawal of the rejection.

In summary, none of the cited references teach or suggest the advantages of the claimed release profile or how to achieve it. The basis for the rejection seems to be that one skilled in the art would have known that certain parameters of PLGA microsphere could be varied to produce different release profiles. The M.P.E.P. states:

> The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (Claims were directed to an apparatus for producing an aerated cementitious composition by drawing air into the cementitious composition by driving the output pump at a capacity greater than the feed rate. The prior art reference taught that the feed means can be run at a variable speed, however the court found that this does not require that the output pump be run at the claimed speed so that air is drawn into the mixing chamber and is entrained in the ingredients during operation. Although a prior art device "may be capable of being modified to run the way [the] . . . apparatus is claimed, there must be a suggestion or motivation in the reference to do so." 916 F.2d at 682, 16 USPQ2d at 1432.

M.P.E.P. § 2143.01, 2100-112 (July 1998). Applicant submit that the claimed invention is far more distinct from the cited references than in the exemplary case of *In re* Mills.

Moreover, viewed as a whole, the cited references establish that researchers working in the drug/antigen delivery area were focused on producing homogenous populations of

microspheres that provided continuous, not triphasic, release of a drug or antigen. The M.P.E.P recognises that such teachings cannot be ignored. The M.P.E.P. explicitly states that if "the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." M.P.E.P. § 2143.01, 2100-113 (July 1998) (citing *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)). Because the modification of the references on which the § 103 rejection is based would change the principle of operation from continuous to multiphasic, the references of record in the present application do not support a case of *prima facie* obviousness.

Conclusion

Applicants respectfully submit that the application is now in condition for allowance. Accordingly, a notice of allowance is respectfully requested. If the Examiner has any questions regarding this submission, the Examiner respectfully requested to telephone and confer with undersigned attorney at (640) 849-4910.

Respectfully submitted,

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